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CHANGES OF CELL ENZYMES, GLUCOSE, CHOLESTEROL AND 17-HYDROXYCORTICOSTEROIDS IN BLOOD DURING PHYSICAL EXERCISE AS A FUNCTION OF THE PHYSICAL TRAINING STATUS

G. Brockkoetter

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16. Abstract

In 11 untrained and 11 highly trained subjects, the alterations of cell enzymes, glucose, cholesterol and 17-OH-corticosteroids were studied in response to physical exercise and as a function of the physical status. The training status was quantified by measuring themaximum oxygen uptake. The two groups of subjects showed differences in their responses to physical exercise with respect to aldolase, glucose and 17-OH-corticosteroids. There was no evidence for a close relationship between the status of physical fitness and the extent of the observed alterations. However, a significant coefficient ($r = 0.628$) was found for the correlation between the maximum oxygen uptake and the plasma aldolase values at rest.

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CHANGES OF CELL ENZYMES, GLUCOSE, CHOLESTEROL AND 17-HYDROXYCORTICOSTEROIDS IN BLOOD DURING PHYSICAL EXERCISE AS A FUNCTION OF THE PHYSICAL TRAINING STATUS

by

G. Brockkoetter

Deutsche Forschungs- und Versuchsanstalt fuer Luft- und Raumfahrt

[German Research and Experiment Institution for Air and Space Travel]

Institut fuer Flugmedizin

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Changes of Cell Enzymes, Glucose, Cholesterol and 17-Hydroxycorticosteroids in Blood During Physical Exercise as a Function of the Physical Training Status*

German Research and Experiment Institution for Air and Space Travel "E.V."**

Institute for Flight Medicine

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Director of Institute:
Prof. Dr. med. S. Ruff

Author:
G. Brockkoetter

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**) Translator's Note: "E.V." = eingetragener Verein = a registered German organization.

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G. Brockkoetter

1. INTRODUCTION

/7*

In an extensive research program in which the work output and stress capacity of highly trained athletes was compared with those of untrained test subjects, the differences in the response of the two groups were studied under conditions of physical exercise. In this connection, we deemed it of interest to determine whether various biochemical parameters also change as a fuction of physical training status.

In particular, it was hoped that the results of this investigation would provide answers to the following questions: 1. Does physical exercise bring about different changes in biochemical parameters as a function of physical training status. 2. Is it possible to draw conclusions regarding the training status of test subjects from the extent of changes in activity and concentration of the biochemical parameters measured by us.

2. LITERATURE REVIEW

/8*

2.1 Enzymes

In view of the concurrent findings of numerous researchers [4, 20, 25, 33, 45, 46, 49, 52, 55, 56, 57, 81, 82, 83] there can be no doubt that physical exercise results in increased cell enzyme activity in blood plasma which depends on the duration and intensity of the physical stress. In contrast to changes in enzyme activity occurring under clinical conditions which may be considered as "extreme", these activity increases are slight and of relatively short duration. The short duration of this "exercise-related enzymatic hyperactivity" ["Arbeitshyperfermentie"] [31] indicates that in this case the phenomenon is not caused by a pathological cell damage but by reversible physiological changes at the cell level. Hess is of the opinion that the anaerobic conditions induced in the skeletal muscles during physical exercise cause an increase in permeability of the cell membrane which allows a fraction of the enzymes to leave the cell [31]. According to Schmidt, on the other hand, we still are entirely in the dark as to the reason for increased enzyme

*Note: Numbers in the margin indicate pagination in the foreign text.

loss during physical exercise and all explanations advanced to date are nothing but assumptions [73].

Several studies have shown that the physical training status affects the extent of the "exercise-related enzymatic hyperactivity". However, the non-uniformity and contradictory nature of the results obtained in this respect are noteworthy. In comparative exercise tests, Richter and Konitzer [64] found that untrained subjects show an increase, trained a decrease, in aldolase activity. Baumann et al [7] obtained similar results when they investigated lactate dehydrogenase activity in trained and untrained subjects after long distance running. Critz and Merrick [19], in their study of glutamate-oxalacetate transaminase by the Harvard step test method, found a decline in activity in both test groups. Only the magnitude of this decline varied, that for the trained subjects being less pronounced than that for the untrained ones. Opposite results were obtained by Fowler et al [23]. Under the same conditions of physical stress on the /9* bicycle ergometer, these workers observed an increase in glutamate-oxalacetate transaminase and malate dehydrogenase activity in both the trained and the untrained test groups. These increases were, on the average, smaller for the trained than for the untrained subjects. Cantone and Ceretelli [15] on the other hand found no differences regarding aldolase activity during and after physical exercise. They did, however, note a dependence of the activity values at rest on training status. With progressive training, these values increased steadily. As a result, trained and untrained subjects showed differences even in initial values. The studies of Richterich et al [65] on transaminases, i.e., glutamate-oxalacetate transaminase and glutamate-pyruvate transaminase, gave similar results. Based on comparison of serum levels, military recruits, after six months of basic training, showed higher average values than did the civilian population. The authors attributed this higher normal level to constantly recurring physical stress during training. According to Calvy [12], after six months of training, the malate dehydrogenase level of marine infantrymen was also higher than that of the civilian population, whereas the lactate dehydrogenase level remained unchanged.

2.2 Blood Sugar

The carbohydrate metabolism plays an important role in physical exercise because, besides the free fatty acids, glucose is an essential energy-producing substrate in skeletal muscle [43]. Numerous investigators [16, 29, 30, 41, 67, 79] have shown that the blood sugar concentration decreases during physical exercise because the increased glucose utilization is not fully compensated by mobilization of the glycogen reserve. The imbalance between utilization and mobilization sets in sooner in untrained subjects and, for equally strenuous exercise, is greater than in trained subjects [17, 42, 44]. The drop in glucose level is seemingly small during short-lasting maximal stress, but quite high /10* during prolonged, steady-state stress. Russian investigators [36, 37] have shown that this could by due in part to the fact that, in short-lasting, very strenuous exercise, the muscle glycogen reserve is also mobilized, whereas under medium-intensity, longer-lasting stress this reserve is not utilized to supply energy requirements. After the exercise, the glucose level increases in all cases. This increase is faster and more pronounced in trained than in untrained subjects [26, 43]. It is due to the fact that, during exercise, glucose mobilization from glycogen reserves is enhanced and that, after cessation of exercise, glucose utilization is reduced. Thus, the glucose level increases as a result of an imbalance between continuing glucose mobilization and reduced glucose

utilization.

2.3 Cholesterol

The widely publicized "Framingham Study" [9], which was carried out on a large group of people, has led to the conclusion that a correlation exists between physical exertion and the cholesterol level in blood. This study has also revealed that in men with a cholesterol level exceeding 269 mg% the risk of myocardial infarction was 3 times higher than in a comparable group with a cholesterol level below 200 mg%. This suggested a direct correlation between physical activity and the development of coronary disease. To date, however, despite numerous studies, this correlation could not be unequivocally demonstrated.

It should be easy to show the effect of physical activity on cholesterol level in blood in a comparative study of trained and untrained subjects. Thus Ahlert [1] found in 56 highly trained athletes a significantly lower cholesterol level at rest than in a comparable group of untrained subjects. Salzmann [71], however, in a study of 211 healthy subjects, could not find a correlation between training status and cholesterol concentration. For quantification of the training status, he determined the maximum oxygen uptake and related it to the blood cholesterol levels. His calculations produced such low correlation coefficients that, in his opinion, a direct correlation can be excluded. Hence, he assumes that blood cholesterol level is affected more by the kind of diet than by physical activity. Campbell [13, 14] in physical training experiments on a bicycle ergometer also could not establish a clear dependence of blood cholesterol level on physical activity. After training, the cholesterol values tended to increase, with fat subjects again showing higher cholesterol concentrations than slim and muscular types. Akguen [2] obtained opposite results when he subjected 19 healthy students to intensive training for a period of three months. At the end of this period, the cholesterol level in these students was significantly lower than in the control group which was examined simultaneously, but which did not undergo the training. This worker's calculations, like those of Salzmann, showed no significant correlation between the drop in cholesterol level and maximum oxygen uptake. Akguen concluded from his experiments that although physical activity of sufficient intensity tends to reduce the cholesterol level, there is no direct correlation between this decline and the physical training status. Dolezel [21] found seasonal differences in the effect of physical training on cholesterol level. After winter training, the cholesterol level was clearly lower whereas after summer training it was slightly but significantly higher. According to Dolezel, this can be attributed to dietary differences as well as to different training methods. /11*

Several workers [38, 53, 68, 69, 79] have found that regardless of training status acute stress in work experiments can cause a change, usually an increase, in cholesterol level. In contrast to changes observed after physical training, however, this increase is only temporary, disappearing within a very short time after cessation of the stress. The magnitude of this increase once again seems to depend on training status. Rochelle [68] and Rotenberg [69] agree in their findings that this increase is significantly higher in the group of trained subjects. /12*

2.4 Corticosteroids

The effect of physical exercise on adrenal function still is unclear despite numerous studies [24, 34, 62, 80]. Animal tests have shown that repeated work stress over a long period leads to adrenal hypertrophy [24, 34]. Removal of the adrenals or hypophysectomy results in adynamia and total inability to perform work [80]. Suzuki [75] was recently able to show, by direct measurement of 17-hydroxycorticosteroids in dog adrenals, that acute work stress leads to increased adrenal secretion. In man, such studies can be performed only by indirect methods. Basically, therefore, all investigations carried out to date used two methods: 1. determination of corticosteroids in blood plasma, and 2. determination of 17-hydroxycorticosteroids or 17-ketosteroids in urine. In this connection, it should be kept in mind that the concentration in blood plasma is at all times a resultant of hormone secretion on the one hand and decomposition, excretion and migration into tissues on the other [39]. The testing of adrenal function by the determination of steroid excretion in urine is also complicated by the fact that the excretionrate depends on intermediate metabolism [27, 62] and kidney output [5, 61].

It is therefore not surprising that the results of studies carried out in man to date are contradictory, particularly in cases where the investigators adopted hormone excretion in urine as the criterion of adrenal activity. Thus, post-exercise corticosteroid excretion was found to be higher [8, 58], lower [35] as well as unchanged [22, 39]. /13*

Data concerning the variation of corticosteroids in blood during physical exercise are still scarce. Here, too, both higher [39] and lower [18] hormone levels were found after physical stress. Nazar [54] points out that these different findings are probably due to differences in the degree of intensity of the work perofrmed. His studies disclosed a decrease in plasma corticosteroids after light exertion on a bicycle ergometer and an increase after exhausting exertion. This contradicts somewhat the view held by Cornil [18] and Kaegi [39] that, with increasing duration of intensity of exertion, the hormone level in plasma must drop because the increased "utilization" by the working muscle prevails over adrenal secretion.

Physical exercise should result in increased adrenal activity in man also [40, 66]. This assumption is based primarily on observations in animal tests [50]. To date, human experiments have not been unequivocal on this point [59]. According to Voigt [77], in trained subjects the average blood concentration of adrenal hormones at rest is higher than in untrained ones. On the other hand, Porthan [58] in his study of 17-ketosteroid excretion found no differences between untrained and trained subjects either at rest or during physical exertion. Alimpic [3] noted in trained subjects after maximal stress a general increase in excretion of 17-hydroxycorticosteroids and 17-ketosteroids in urine; however, this increase was the smaller the higher the work capacity achieved. Israel [35] reported similar results for highly trained bicycle racers, i.e., those in better physical condition showed lower excretion of 17-ketosteroids. Finally, Brdaric [11] studied the excretion of 17-hydroxycorticosteroids and 17-ketosteroids in the /14* course of systematic physical training. He found that the excretion rate increased with improving physical training status. For this reason, he believes that physical training stimulates adrenal activity.

3. METHODOLOGY /15*

3.1 Test Subjects and Test Arrangement

The studies were conducted on two groups of volunteers who were financially rewarded for their cooperation. The first group consisted of 11 healthy, untrained students. The second group consisted of 11 trained subjects. Most of these were athletes of national or international all-star caliber in their respective disciplines (long-distance running, obstacle racing, bicycle racing, ice skating). Each of the two groups was subjected to two work capacity tests on the bicycle ergometer according to the method of Mueller [51]. The first test, under most intense work conditions, served to determine maximum oxygen uptake; the second test, under conditions of average work intensity, served for the study of the biochemical parameters.

Maximum oxygen uptake ($VO_{2\ max}$) was determined by the method of Hollmann [32], the untrained group starting at 13 kg m/sec*, the trained group at 21 kg m/sec. Then the work intensity was constantly increased, every three minutes, in steps of 2 kg m/sec until the individual maximum was reached. The average work capacity attained was 24 kg m/sec for untrained subjects and 34 kg m/sec for trained ones.

The duration of the average physical stress was 30 min in all cases. To subject both test groups to a comparable stress, the work intensity selected was 50% of the average maximum work capacity attained, i.e., 12 kg m/sec for the untrained group and 17 kg m/sec for the trained subjects.

Four blood samples were drawn for the determination of biochemical parameters: the first immediately before the start of work, the second 10 min later, the third 30 min and the last 90 min after the start of work. The blood was drawn from the cubital vein under conditions of unimpeded blood flow and heparinized. All tests were carried /16* out at the same time of day, between 1 and 5 p.m., to exclude the effect of possible periodic daily fluctuations.

3.2 Chemical Methods of Determination

Enzymes, 17-hydroxycorticosteroids, total cholesterol and total protein were measured in the plasma, whereas blood sugar was determined in whole blood. The results are expressed in the following units: enzyme activity in mU/ml, blood sugar and total cholesterol in mg per 100 ml (mg%), corticosteroids in μg per ml (μg%) and total protein in g per 100 ml (g%). The following methods were used.

3.2.1 Enzymes

By means of the test scheme of the Boehringer company, Mannheim [10], the activity of the following enzymes was determined: fructose-1, 6-diphosphate aldolase (ALD), glutamate-oxalacetate transaminase (GOT), glutamate-pyruvate transaminase

*Translator's Note: The German "kp" = kilopond = kg_{force}.

(GPT) and malate dehydrogenase (MDH). These optical tests involve the measurement of light absorption by a coenzyme taking part in a reaction. In our case, the coenzyme was nicotinamide adenine dinucleotide (NAD). The reduced form (NADH) has an absorption maximum at 340 nm, whereas NAD (oxidized form) shows no absorption in the 300-400 nm range. Hence, NAD-dependent dehydrogenase reactions can be followed photometrically in this wavelength range by measuring either an increase in absorbance (formation of NADH with a decrease in NAD) or a decrease thereof (formation of NAD with a decrease in NADH). The same is true for reactions in which the reaction products can be determined by NAD-dependent enzyme reactions (indicator reactions). The activity of glutamate-oxalacetate transaminase and glutamate-pyruvate transaminase is measured by combining the reactions catalyzed by these enzymes with an indicator reaction catalyzed by a dehydrogenase (malate or lactate dehydrogenase) and involving NAD as the coenzyme. The aldolase assay involves the use of an auxiliary reaction which is interposed between the aldolase catalyzed reaction and the corresponding indicator reaction (glycerophosphate dehydrogenase). This auxiliary reaction is also enzyme-catalyzed (auxiliary enzyme: triose phosphate isomerase). /17*

The activity of an enzyme is characterized by the reaction rate. The measure of enzyme activity is the international unit. This unit is defined as that quantity of enzyme which, under optimal measuring conditions, brings about the reaction of 1 mole of substrate per minute at 25° C. This unit is indicated by the synbol U (unit) and one thousandth thereof by mU (milliunit) [60, 63].

3.2.2 Blood Sugar

The sugar assay was performed by the test scheme of Boehringer, Mannheim [72]. This assay is based on the enzymatic determination of "true glucose" and involves the oxidation of glucose to gluconolactone by means of the specific enzyme glucose oxidase. In aqueous solution, the lactone is converted into gluconic acid. This reaction produces hydrogen peroxide which in the presence of peroxidase brings about the dehydrogenation of o-dianisidine to a red-brown dye. The intensity of the resulting color is proportional to the glucose concentration and is measured at a wavelength between 430 and 480 nm.

3.2.3 Cholesterol

Total cholesterol was determined by the method of Mann [48] which involves saponification of esterified cholesterol followed by extraction from the plasma of the cholesterol thus liberated together with the pre-existing free cholesterol fraction. The Zlatkis color test was carried out with iron (III) chloride in concentrated sulfuric acid, and the absorbance was measured at 560 nm in a photometer.

3.2.4 17-Hydroxycorticosteroids

Free 17-hydroxycorticosteroids in blood plasma were determined fluorometrically by the method of Laughlin [47]. The plasma was extracted with dichloromethane, and the 17-hydroxycorticosteroids were separated from this extract chromatographically on a silica gel column. The 17-hydroxycorticosteroids purified in this manner were /18*

converted to the corresponding "fluorophors" in sulfuric acid solution and measured in the fluorometer. Excitation occurred at 470 nm, and fluorescence was determined at 530 nm. A filter was used to eliminate stray radiation.

3.2.5 Total Protein

Total protein in blood plasma was determined by means of the kit supplied by the Haury company, Munich. The method is based on a standardized biuret test procedure.

3.3 Abbreviations and Normal Values

For purposes of clarity, the abbreviations used in the tables, figures and text to denote the parameters tested are again listed below. Also given are their normal values as determined by the assay methods used by us.

Abbreviation		Normal value
ALD	fructose-1, 6-diphosphate aldolase	(up to 6 mU/ml)
GOT	glutamate-oxalacetate transaminase	(up to 12 mU/ml)
GPT	glutamate-pyruvate transaminase	(up to 12 mU/ml)
MDH	malate dehydrogenase	(48-96 mU/ml)
BS	blood sugar	(50-95 mU mg %)
CH	total cholesterol	(120-250 mg %)
CS	17-hydroxycorticosteroids	(6-24 µg/100 ml)
TP	total protein	(6.5-8.0 g %)

3.4 Statistical Procedures

Mean values and standard deviations were calculated by known methods [28, 70]. To obtain the stress reaction, the individual differences between initial values and values under stress were calculated and expressed as per cent of the initial value. The significance of the differences was checked by Student's test, the method of paired comparisons being used for intraindividual differences and the method of independent random variables for interindividual differences. Differences for which the test gave a probability $P = 0.05$ were considered as significant. To test for the existence of a linear relationship between two parameters, the Pearson product-moment coefficient of correlation was calculated.

The statistical symbols used were as follows: $\bar{x}$ = mean; $\Delta\bar{x}$ = difference between means; S.D. = standard deviation; P = probability; r = linear correlation coefficient; t = test quantity*.

*The author wishes to thank Graduate Meteorologist G. Caroli of the Physiological Institute, University of Bonn (Director: Prof. Dr. med. J. Pichotka) for the courtesy of reviewing the statistical results.

4. RESULTS /20*

4.1 Age, Weight, Body Measurements and Maximum Oxygen Uptake

Table 1 summarizes the age, weight, body measurements and maximum oxygen uptake data for both test groups. As expected, the maximum oxygen uptake data show large and highly significant differences. For the trained subjects, the oxygen uptake value for the whole body is more than 35%, and taking into account weight differences, 47.8% higher than the value for the untrained group. This clearly illustrates the great difference in training status between the two groups.

4.2 Initial Values and Values Under Stress for Untrained Subjects

For the untrained subjects, the absolute initial values of the blood parameters and their relative change under stress, expressed in per cent, are given in Table 2. A direct comparison with normal values shows that all initial values with the exception of MDH lie within the normal range. The MDH value of 47.2 mU/ml is just below the lower limit indicated by Boehringer, Mannheim [10]. Note, however, that for practical reasons our enzyme activities were determined in blood plasma, whereas the cited normal range refers to blood serum. Studies of Solbach [74] and Vetter [76] have shown that on the average 17-40% lower values are obtained when the determination is carried out in plasma. This is because additional enzyme activity is released from the disintegrating cells during serum work up. This provides an adequate explanation of the low MDH values found.

In the untrained group all parameters with the exception of blood sugar increased during stress (12 kg m/sec). The increase in corticosteroid concentration is not significant in view of the marked individual scatter. Blood sugar dropped rapidly and clearly during the first ten minutes of test. During the following 80 min, it tended to assume pre-exercise values. ALD, MDH and CH attained their maximum values within 10 min following the start of exertion, whereas GOT and GPT showed maximum increase in activity after 30 min. MDH showed the greatest increase relative to the initial value, i.e., 30%. The changes in GOT and GPT activities dropped to about 10% below the initial value and the aldolase and cholesterol values increased to about 12% above this value. /23*

To check the blood concentration, each blood sample was analyzed for total protein, hematocrit, erythrocyte count and hemoglobin concentration. It is assumed that any changes in total plasma volume or in the relative volume of plasma and blood cells in peripheral blood are reflected in the variation of these quantities. Their determination thus provides information about the extent to which the stress responses of the biochemical parameters represent "real" changes as compared to variations caused merely by changes in blood concentration. An increase in total protein concentration clearly shows that within the first 10 minutes total plasma volume dropped by more than 10% during the physical exercise. By the end of this exercise, the initial change was compensated by about one-half (4.6%, 30 min). A similar situation is thought to exist as regards peripheral blood: hematocrit, erythrocyte count and hemoglobin values show that here, too, the blood concentration changes, i.e., the plasma volume undergoes a relative decrease and both the cell volume and cell number undergo a relative increase. These findings show that up to 10% of the increases in concentration and activity of the quantities

TABLE 1 AGE, WEIGHT, BODY MEASUREMENTS AND MAXIMUM OXYGEN UPTAKE (UNTRAINED COMPARED TO TRAINED SUBJECTS)

	Untrained (n = 11)		Trained (n = 11)		
	$\bar{x}$	S.D.	$\bar{x}$	S.D.	t
Age, years	23,91	1,76	27,36	2,84	-3,4249 **
Weight (kg)	75,09	4,83	69,73	5,82	2,3514 *
Height cm	182,00	3,29	177,00	6,24	2,3509 *
Surface area, m^2	1,95	0,06	1,86	0,10	2,8398 **
VO_2 max lit/min	3,24	0,26	4,52	0,47	-7,9210 ***
VO_2 max (ml/kg/min)	43,10	2,86	65,41	5,36	-12,1279 ***

t	P	
3,850	0,001	(***)
2,845	0,01	(**)
2,086	0,05	(*)

TABLE 2 INITIAL VALUES AND THEIR CHANGES DURING AND AFTER PHYSICAL STRESS (12 kg m/sec, 30 min) IN THE UNTRAINED GROUP (n = 11).

	Normal values	Initial values		Mean changes in per cent				
			S.D.	10min	P	30min	P	90min	P
ALD	(up to 6 mU/ml)	3,13	0,3	12,5	0,01	12,2	0,02	3,5	0,50
GOT	(up to 12 mU/ml)	8,15	1,8	14,5	0,005	20,0	0,01	1,8	0,70
GPT	(up to 12 mU/ml)	4,60	2,7	9,3	0,02	18,9	0,005	13,9	0,30
MDH	(48 - 96 mU/ml)	47,18	8,4	31,0	0,001	29,4	0,001	10,7	0,20
BS[a)]	(50 - 95 mg%)	88,10	13,8	-19,3	0,005	-6,4	0,30	-2,2	0,50
CH	(120 - 250 mg%)	195,40	34,8	12,7	0,001	10,1	0,001	3,4	0,40
CS	(6 - 24 µg/100 ml)	14,50	3,1	3,4	0,70	17,4	0,20	-6,8	0,40
TP[b)]	(6,5 - 8,0 g%)	7,69	0,9	10,6	0,001	4,6	0,001	-1,4	0,50
ERY[c)]	(4,5 - 5 mil./mm^3)	4,80	0,3	4,8	0,005	3,7	0,001	-0,5	0,70
HA[d)]	(40 - 48 Vol%)	42,10	2,1	6,2	0,005	3,1	0,10	-2,0	0,40
HB[e)]	(14 - 15 g/100ml)	14,50	0,8	5,5	0,001	3,8	0,001	-1,5	0,10

a) BS = blood sugar; b) TP = total protein; c) HA = hematocrit; d) ERY = erythrocyte count; e) HB = hemoglobin content.

measured in plasma after 10 min and up to about 5% of those measured after 30 min are due to changes in blood concentration alone. From a comparison with the relative increase in GPT (9.3%), ALD (12.5%) and CH (12.7%) after 10 min, it is concluded that these changes are due essentially to a drop in total plasma volume. The situation /24* after 30 min is different. The significant increases observed in this instance are much greater than the changes of the "blood concentration parameters" and, hence, could, at least to a large extent, represent "real" increases in concentration.

4.3 Initial Values and Values under Stress for Trained Subjects

Table summarizes the data for the trained group. Normal values are also given. A comparison with initial values shows that all values for this test group including MDH lie within the normal range. It is noteworthy that the initial enzyme activities are higher than for the untrained group. However, this is in accord with the results of other workers [12, 15, 65] who found higher GOT, GPT and ALD levels in trained subjects than in similar untrained groups. Other differences between the test groups will be discussed in greater detail later.

In general, this group also shows increases in activity and concentration except for blood sugar. However, here the changes in aldolase activity are not significant. The blood sugar at the start of exertion tends to drop slightly, but this change is so small as to be statistically insignificant. The maximum GOT and GPT values were attained after 10 min whereas MDH, CH and CS attained a maximum after 30 min. This increase in corticosteroid concentration (31.7%, 30 min) is striking. GPT and MDH also showed clear-cut increases (23.2% and 14.1%, respectively), whereas the other parameters increased by less than 12%.

The trained subjects also show a significant change in blood concentration as indicated by the variation of total protein values, hematocrit and erythrocyte count. These variations are similar in magnitude to those for the untrained group, but here normal levels seem to be established more slowly. A comparison of the 10 min values shows /26* clearly that most of the level rises observed can be attributed to a drop in total plasma volume. Only GPT and MDH show an additional absolute increase. The 30-min values also show a strong effect of the blood concentration on the changes measured. However, the increase in MDH activity and corticosteroid level definitely reflect an absolute increase in concentration.

4.4 Effect of Training Status on Group Comparison

Table 4 which lists the differences of the means ($\Delta\bar{x}$) between untrained and trained subjects, permits a closer comparison of the two test groups. In this table, a negative sign indicates that the mean for the trained group is higher than that for the untrained group, while a positive sign indicates the opposite.

The small number of significant differences between the two groups is striking. This is attributable in part to the fact that the differences are small and in part to considerable scatter of the means.

TABLE 3 INITIAL VALUES AND THEIR CHANGES DURING AND AFTER PHYSICAL STRESS (17 kg m/sec, 30 min) IN THE TRAINED GROUP (n = 11)

	Normal values	Initial values		Mean changes in Percent					
			S.D.	10min	P	30min	P	90min	P
ALD	(up to 6 mU/ml)	4,75	0,9	8,6	0,20	4,0	0,40	-7,2	0,01
GOT	(up to 12 mU/ml)	10,70	2,1	11,9	0,05	8,5	0,05	-2,7	0,40
GPT	(up to 12 mU/ml)	6,08	2,5	23,2	0,05	9,4	0,20	3,8	0,60
MDH	(48 - 96 mU/ml)	51,22	8,5	14,1	0,02	18,2	0,02	14,4	0,20
BS[a]	(50 - 95 mg%)	87,70	17,0	-2,6	0,50	7,7	0,20	0,7	0,80
CH	(120 - 250 mg%)	198,00	20,8	7,8	0,01	9,2	0,02	1,7	0,30
CS	(6 - 24 µg/100 ml)	13,50	2,3	11,1	0,20	31,7	0,02	11,1	0,20
TP[b]	(6,5 - 8,0 g%)	7,37	0,5	11,4	0,001	8,1	0,001	4,2	0,01
ERY[c]	(4,5 - 5 mil./mm^3	4,70	0,5	6,1	0,001	4,7	0,001	0,7	0,30
HA[d]	(40 - 48 Vol%)	43,40	3,2	6,8	0,001	4,6	0,001	1,1	0,70
HB[e]	(14 - 15 g/100 ml)	14,40	1,0	7,3	0,001	5,9	0,001	0,2	0,90

a) BS = blood sugar; b) TP = total protein; c) HA = hematocrit; d) ERY = erythrocyte count; e) HB = hemoglobin content.

TABLE 4 DIFFERENCES BETWEEN MEANS ($\Delta\bar{x}$) FOR UNTRAINED AND TRAINED SUBJECTS. (INITIAL VALUES ARE GIVEN IN ABSOLUTE TERMS, VALUES UNDER STRESS IN PERCENT)

	Initial values		10-min values		30-min values		90-min values	
	$\bar{x}$	t	$\bar{x}$	t	$\bar{x}$	t	$\bar{x}$	t
ALD	-1,45	-8,197***	3,90	0,638	8,20	1,396	10,60	1,800
GOT	-2,45	-2,213*	2,54	0,426	11,50	1,628	4,50	0,841
GPT	-1,44	-1,732	-13,80	-1,733	9,50	1,227	10,10	0,764
MDH	-4,04	-0,919	16,90	2,432*	11,20	1,294	-3,70	-0,304
BS	0,40	0,061	-16,70	-2,797*	-14,10	-1,894	-2,90	-0,866
CH	-2,59	-0,212	4,90	1,414	0,86	0,197	1,71	0,500
CS	1,00	0,859	-7,66	-0,812	-14,30	-0,929	-17,90	-1,920

t	P	
3,850	0,001	***
2,845	0,01	**
2,086	0,05	*

The trained subjects consistantly show higher enzyme activity values at rest than do the untrained ones; however, only the differences for aldolase and GOT are statistically significant. With the exception of GPT after 10 min and MDH after 90 min, the values for the untrained group are higher. However, this general trend toward higher values is statistically significant only for MDH after 10 min.

The blood sugar, cholesterol and corticosteroid levels at rest do not reflect an influence of training status. The differences between the two groups are so small that the means may be considered as being practically identical. The difference in training /28* status shows an effect only on values determined under stress conditions. For the untrained group, the blood sugar clearly declines at the start of physical work (10 min) to statistically lower values than for the trained group. This trend toward lower blood sugar levels persists for the untrained subjects to the end of the exercise, the differences disappearing only after termination of physical exercise. The cholesterol level increases significantly under stress in both groups. The magnitude of this increase is practically equal for both groups, as indicated by the small differences between the means. The tendency of trained subjects to show higher corticosteroid levels under stress is noteworthy. Some of the means are considerably higher than for the untrained group. The individual scatter of hormone concentrations is, however, so pronounced for both groups that it is impossible to establish that the difference observed is a function of training status.

Figures 1 and 2 give a graphic representation of the data of Table 4. Figure 1 shows clearly that trained subjects differ from untrained ones in that they react to physical /29* exercise almost exclusively by a less pronounced increase in enzyme activity. Exceptions are GPT 10 min and MDH 90 min after the start of exercise.

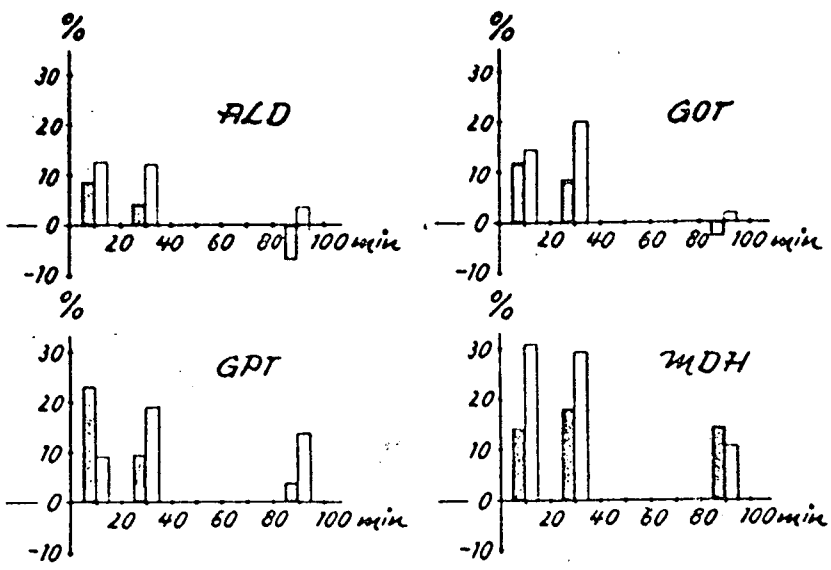

Figure 1 Per cent change in enzyme activity from initial value measured during and after physical stress
Comparison: trained (■) vs. untrained (□) subjects

Figure 2 shows the differences in the variation of blood sugar and corticosteroid levels for the two test groups. For the untrained group, the blood sugar level drops markedly under stress, whereas for the trained group this level remains relatively constant. As regards the corticosteroids, the trained group clearly tends to show higher blood levels during and after stress. The graphic representation of the cholesterol changes once again shows clearly the absence of any differences between the two test groups.

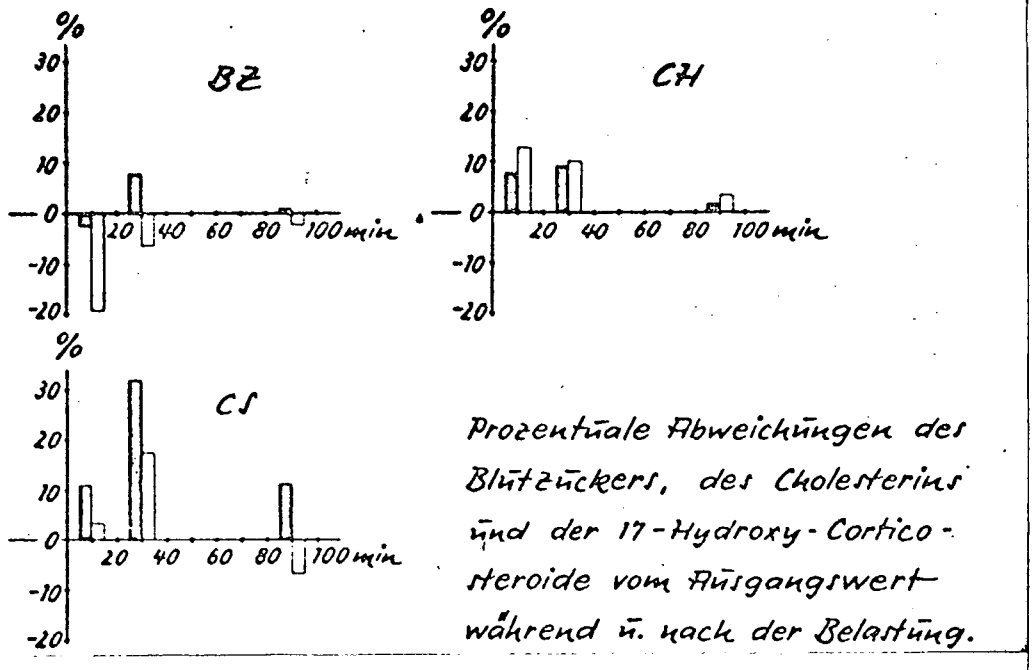

Figure 2 Percent change in blood sugar, cholesterol and 17-hydroxycorticosteroids from initial value measured during and after physical stress. Comparison: trained (■) vs. untrained (□) subjects.

4.5 Effect of Training Status on Individual Comparisons /30*

In the foregoing, the effect of physical training on the biochemical parameters was investigated by comparing two groups of subjects differing clearly in training status. The data in Table 5 provide the individual comparisons. To this end, the two test groups were combined into a single population. The training status of an individual subject was expressed numerically in terms of maximum oxygen uptake, both with and without regard for body weight. To provide an individual correlation between training status and the variation of the various parameters, the correlation coefficient was calculated for the relationship between maximum oxygen uptake on the one hand and the initial values and values under stress on the other. The results are summarized in Table 5.

TABLE 5 CORRELATION COEFFICIENTS (r) FOR THE RELATIONSHIP BETWEEN MAXIMUM OXYGEN UPTAKE (IN LITERS PER MIN AND ML PER KG OF BODY WEIGHT [PER MIN]) AND THE INITIAL VALUES AND VALUES UNDER STRESS CONDITIONS FOR INDIVIDUAL BLOOD PARAMETERS (UNTRAINED AND TRAINED SUBJECTS COMBINED, n = 22)

	ALD	GOT	GPT	MDH	BZ	CH	CS	
VO_2 max (l/min)	0,628**	0,597**	0,468*	0,295	-0,090	0,104	-0,069	Initial values
VO_2 max (ml/kg/min)	0,695***	0,603**	0,353	0,173	-0,021	0,078	-0,180	
VO_2 max (l/min)	-0,131	-0,085	0,274	-0,517*	0,341	-0,301	-0,191	10-min values
VO_2 max (ml/kg/min)	-0,094	-0,129	0,304	-0,484*	0,449*	-0,296	0,202	
VO_2 max (l/min)	-0,283	-0,239	-0,327	-0,107	0,446*	-0,114	0,169	30-min values
VO_2 max (ml/kg/min)	-0,260	-0,320	-0,355	-0,197	0,334	-0,169	0,280	
VO_2 max (l/min)	-0,462*	-0,421	-0,179	0,141	0,186	-0,099	0,303	90-min values
VO_2 max (ml/kg/min)	-0,463*	-0,124	-0,252	0,034	0,195	-0,173	0,424*	

r	P	
0,652	0,001	***
0,537	0,01	**
0,423	0,05	*

The frequent incidence of significant coefficients among initial enzyme activity values is striking. The magnitude of the coefficients reveals a clear-cut correlation between ALD and GOT and maximum oxygen uptake, while for GPT this correlation is not as definite. Moreover, the positive sign of the coefficients confirms the rule, previously established for the group comparison, that the more highly trained subjects show higher enzyme activities at rest. This obviously does not apply to MDH for which the relatively low coefficient precludes the existence of a close correlation. All correlation coefficients for the enzyme values under stress are negative with the exception of GPT (10 min) and MDH (90 min). These data indicate, as did those of Table 4, a reversal of the rule established for initial values. In other words, the more highly trained subjects tend to show lower values under stress. However, the coefficients show clearly that this correlation is not statistically significant. Only ALD (90 min) and MDH (10 min) show a significant, reasonably straight-line correlation with the maximum oxygen uptake.

The initial blood sugar, cholesterol and corticosteroid values show practically no /32* linear correlation with maximum oxygen uptake. The unusually low coefficients confirm the findings based on group comparison, that training status has no appreciable effect on these levels at rest. For some parameters, a correlation appears under conditions of stress. Thus, the blood sugar values after 10 and 30 min show a significant, positive correlation with maximum oxygen uptake. Obviously, body weight also plays a role in this case. This is indicated by the fact that these coefficients change markedly when body weight is taken into account. The constancy of the negative coefficients for the cholesterol levels under stress conditions suggests a certain regularity of relationship with maximum oxygen uptake. On the other hand, however, the calculated coefficients are so low that for all practical purposes they preclude the existence of a close correlation or at least of a close linear correlation. Finally, the corticosteroid level shows a significant correlation only after 90 min. The correlation calculation thus does not reflect the observed tendency of trained subjects to show higher values under stress also after 10 and 30 min. The reason for this could be the large individual scatter range observed for the response of corticosteroids to physical work in both test groups. The correlation becomes more definite only after cessation of the exertion. The correlation coefficient for the 90 min values indicates a slight but statistically significant correlation with maximum oxygen uptake. Accordingly, at this point in time, the more highly trained subjects tend to show higher corticosteroid levels. The group comparison also suggested this, but the finding was not statistically significant.

5. DISCUSSION OF THE RESULTS /33*

If we define as physical work capacity the ability to perform work aerobically under maximum stress, then the maximum oxygen uptake is the parameter that provides direct information about work capacity. According to Hollmann [32], the maximum oxygen uptake is a quantity "that reflects the over-all capacity of respiration, blood, circulation and skeletal muscles to perform work". By systematic training, it is possible to enhance the maximum work capacity, expressed in terms of VO_2 max, by 50% of the initial value. Physical exercise on the bicycle ergometer when carried out at 50% of the maximum individual work capacity produces measureable changes in the parameters studied by us. This statement is generally valid regardless of the training status, but it does not apply to all parameters measured. Exceptions are the aldolase, blood sugar and corticosteroid values which, under conditions of physical stress, either show

statistically significant changes only in the untrained group (aldolase, blood sugar) or only in the trained group (17-hydroxycorticosteroids). This provides an answer to the first of the questions posed in the introduction: At least three of the parameters studied by us show variations which depend on the average training status of the two test groups. Finally, the initial values also show differences as a function of training status. This, of course, is true only for the enzyme activities studied by us. At rest, the more highly trained subjects definitely show higher plasma enzyme levels. For the remainder of the parameters studied, the means for the two groups differ so slightly that they may be considered as being identical.

To find an answer to the second of the initially posed questions on the basis of our results is more difficult. Although, as previously mentioned, differences in magnitude of the parameter changes have been shown to depend on training status, these differences seemingly cannot be correlated directly with the maximum oxygen uptake. This is indicated by our correlation calculations. Only a few statistically significant coefficients were /34* found for the correlation between maximum oxygen uptake and parameter values under stress conditions. Furthermore, these coefficients are so low that, in our opinion, it is not possible to draw from the magnitude of these changes any definite conclusions about the training status. This general statement does not apply to the results concerning aldolase which will be discussed later.

The mechanism underlying the increase in activity of cell enzymes in blood in response to physical exercise is not entirely clear. There are indications which suggest that muscular exercise can bring about an increase in membrane permeability of muscle cells [31]. Higher requirements placed on cell metabolism could interfere with the supply of energy needed for maintaining membrane density. Thus, the higher level of cell enzymes in blood could be attributed to a negative energy balance in cell metabolism. Based on our findings, we may then assume that trained subjects for whom the increase in enzyme activity is generally smaller than for the untrained subjects, have acquired the ability to equalize more readily the energy balance of their muscle metabolism during physical work. The reverse situation regarding enzyme activities at rest seems to contradict this hypothesis. The differences between means and the correlation calculations both show clearly that the more highly trained subjects tend strongly toward appreciably higher values at rest than do the less trained or untrained subjects. This observation is in agreement with the findings of many investigators [12, 15, 65]. Although we are, to an extent, justified in considering the muscle cell as the main source of "work-related enzyme hyperactivity" in plasma, there is no doubt that numerous other enzyme-rich tissues also contribute to plasma enzyme levels at rest or under normal conditions [31]. It is therefore difficult to explain why trained subjects should show /35* higher enzyme levels at rest. It is conceivable that this is due to differences in muscle mass. Cantone [15] postulates that the muscle cell is capable of meeting the constantly elevated energy requirements during training also because of an induced increase in enzyme production. This generates a higher concentration gradient between cell and plasma and, as a direct result, increased enzyme levels in blood. This view is consistent with our explanation of the reverse situation during exercise: The concentration gradient is not affected by short-lasting physical effort so that the ability to supply adequately total energy requirements becomes determining under these conditions. Higher enzyme concentrations are useful in this respect because by increasing the conversion rates they promote faster utilization of available energy carriers. It is not possible to conclude firmly at this time whether these concepts are realistic.

The change in blood sugar levels during muscular work has been explained [6]. This change not only depends on the intensity and duration of work, but also on training status. Typical for untrained subjects is an initial drop, which is the greater the more strenuous the effort. Under steady-state work conditions, the sugar level tends to return to normal values. By contrast, trained subjects show greater constancy during light or semi-strenuous work; marked hypoglycemia is observed only under conditions of fatigue. In view of these differences, it is surprising that our results do not show a closer correlation between maximum oxygen uptake and the change in blood sugar level during work. Correlation coefficients $r = 0.449$ (10 min) and $r = 0.446$ (30 min) are significant thus indicating the existence of a correlation. However, their value is so small that at this time they permit no general conclusions regarding changes in blood sugar as a function of training status. As shown by Keul et al [42], the differences between untrained and trained subjects are still greater when the blood sugar is measured /36* in arterial blood. Conceivably, corresponding calculations based on such measurements would show a closer correlation than do the blood sugar values in venous blood determined by us.

Based on our results, the cholesterol level shows no differences owing to training status neither at rest nor during exercise. In its response to stress in both groups the cholesterol level clearly follows changes in hematocrit and total protein. Since 75% of blood cholesterol is bound to lipoproteins, the increased levels observed are not absolute increases but essentially relative increases in concentration caused by a drop in total plasma volume. These findings contradict the observations of other investigators which suggest that physical activity leads to a decline in cholesterol level [1, 57] and that trained subjects show under conditions of acute physical effort a different change in cholesterol level than do untrained subjects [68, 69]. To a large extent, this discrepancy can be explained on the basis that it is not always absolutely clear what is meant by different training status. To define the training status, subjective statements are frequently made in the literature regarding the intensity and duration of training of the test subjects. It is noteworthy that whenever the training status was quantified by maximum oxygen uptake, no correlation between cholesterol and physical training could be established [2, 13, 14, 71].

The concentration of 17-OH-corticosteroids in peripheral blood is a resultant of several factors: 1. secretion; 2. distribution and dilution in the intravasal space; 3. metabolism; 4. excretion [39]. Moreover, an increased "utilization" by the working muscle is thought to affect the plasma level by acting in opposition to secretion [18, 50]. The marked scatter of our findings suggests that the large interindividual differences /37* depend on the extent to which these individual factors are involved. This would also explain why the unusually high (in an absolute sense) increase in 17-OH-corticosteroids in response to muscular exercise found by us is not statistically significant. Only the trained group showed a significant increase of 31.7% at the end of physical stress. This value represents in absolute terms the largest change measured by us. Interestingly, trained subjects generally showed higher corticosteroid levels under stress than did untrained subjects, the values at rest or the initial values being practically identical for both groups. A more pronounced response to stress in trained subjects has been reported also for other types of stress (acceleration, oxygen insufficiency) [78]. From the fact that in such instances, too, the levels at rest showed no differences, it was assumed that trained subjects as a result of constantly repeated stimulation by physical stress have acquired a higher non-specific "adrenal reactivity" compared to untrained subjects. Whether this assumption is correct cannot be decided here. It is noteworthy,

however, that our results sometimes show no significant correlation whatever between maximum oxygen uptake and 17-OH-corticosteroid changes during exercise (10 and 30 min) and sometimes only a very small, statistically significant coefficient ($r = 0.424$; 50 min after cessation of exercise). This leads to the conclusion that the hypothesis adopted in the case of oxygen insufficiency and acceleration cannot be applied directly and with equal justification also to physical exercise.

With respect to the questions posed in the introduction, aldolase gave by far the most interesting results among the parameters studied by us. For this reason, we left the detailed discussion of these results for the end. According the Richter and Konitzer [64], in the work capacity test serum aldolase activity increases in untrained subjects and decreases in trained ones. In our experiments, too, 60 min after cessation of work aldolase activity intrained subjects tended to decrease -7.2% below the initial value. This value, for which $P = 0.1$, is at the limit of statistical significance. This difference as a function of training status is supported by our correlation calculation. By combining the two test groups into one population and calculating the correlation coefficient for the relationship between maximum oxygen uptake and aldolase values for 60 min after cessation of exercise (90 min values), a significant negative coefficient is obtained. This coefficient is not very large, pointing to a moderately linear relationship. However, in this instance, too, physically untrained subjects tend to show higher aldolase activities than do trained ones. /38*

The aldolase values at rest show still more pronounced correlation with training status. This correlation is characterized by a reversed sign. At rest, trained subjects on the average show higher aldolase levels than do untrained ones. The high statistical significance leaves no doubt that this difference is not due to chance. The relatively high correlation coefficient ($r = 0.695$) for the individual comparisons between maximum oxygen uptake and initial aldolase values supports this conclusion. This correlation not only reflects the clear-cut difference between the two test populations, but particularly the existence of a linear relationship between training status improves the aldolase level at rest increases. This result is in good agreement with the observations of Cantone and Ceretelli [15] and reinforces them in that it is statistically significant. The correlation established by us suggests that, in analogy to the method of determining maximum work capacity by measuring maximum oxygen uptake, it should be possible to use the determination of aldolase activity in blood as a means for obtaining quantitative information about the training status. This would be particularly valuable from a practical standpoint: The method of determining maximum oxygen uptake which is technically relatively tedious and time-consuming would be replaced by a very simple, rapid chemical assay; furthermore, the subject would not be subjected to stress since the assay would be conducted at rest and not under exhausting exercise conditions. In our opinion, however, the results presented here do not allow such a general conclusion for the following reason: The correlation expressed by the coefficient $r = 0.695$, calculated by us is not sufficiently linear to provide a reflection of aerobic work capacity. Moreover, the population sample studied is too small to justify a general conclusion which would be applicable outside this population. On the other hand, we believe that our results are sufficiently important to provide a new, promising basis for further studies. /39*

6. CONCLUSION

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Changes in enzymes, glucose, cholesterol and 17-hydroxycorticosteroids were studied in the blood of 11 untrained and 11 trained test subjects during physical work. For both groups, maximum oxygen uptake was used as the criterion of physical work capacity and hence training status. The results show that under standardized work conditions, aldolase activity and blood sugar and corticosteroid levels vary depending on training status. From the magnitude of the changes induced by physical stress, no definite conclusions can be drawn regarding physical work capacity. It is assumed that a closer correlation exists between aldolase activity at rest and training status. This is based on the fact that the correlation coefficient calculated for the relationship between maximum oxygen uptake and aldolase activity is $r = 0.628$.

Gerd Brockkoetter
Institut fuer Flugmedizin
53 Bonn — Bad Godesberg
Koelner Strasse 70

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